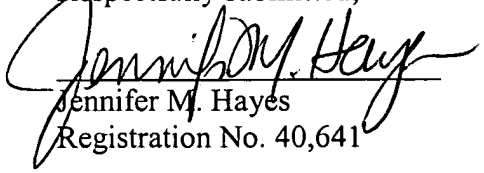
As can be seen from the claims, the present pharmaceutical composition is characterized by a combination of (1) comprising one or more water-soluble and/or low water soluble substance, and (2) having an osmotic pressure of less than 290 mOsm. Only when both characteristics (1) and (2) are simultaneously satisfied, is the high bioavailability of the present invention obtained. This is clearly shown in the examples in the present specification and further clarified in the attached Explanation. With respect to the composition disclosed by Kim, Applicants were unable to measure its bioavailability.

Applicants also submit substitute drawings of Figures 1, 2 and 3 which more accurately reflect the results for the relevant compositions in the specification. Applicants formally request approval of the substitute drawings.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Applicant hereby petitions for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,



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Date: November 14, 2001

Attachment

09/446276

Summary of Data in our specification

1. Subject matter of the summary

Subject matter (1)

Claim 1 elements:

- Low water soluble or water insoluble substance
- Medicament
- Osmotic pressure of less than 290 mOsm

(page 29, lines 2 to 6)

Superiority of this invention over conventional arts:

- Markedly efficient and high permeability

(page 6, lines 30 to 35)

Subject matter (2)

Amended claim 3 elements (in case containing hemostatic agent):

- Low water soluble or water insoluble substance
- Medicament
- Osmotic pressure of less than 290 mOsm
- hemostatic agent

(page 29, lines 10 to 14)

Superiority of this invention over conventional arts:

- Retentivity of medicament at the mucosa

(page 6, lines 30 to 35)

2. Comparison of examples and comparative examples concerning subject matter (1)

i. Example 1 and Comparative example 1 (page 12, line 36 to page 16, line 3)

Medicament: Fluorescein

A model drug of the liposoluble low molecular weight drug

- Osmotic pressure of less than 290 mOsm unexpectedly increased the medicament bioavailability.
- Low water soluble or water insoluble substances were necessary to increase the medicament bioavailability and the bioavailability increased accompany with the low water soluble or water insoluble substance concentration increase up to 1.5%w/w.

Composition No.1-4 and 11

(Osmotic pressure-controlling agent : Sodium chloride)

Composition No.	1	2	3	4	11
Sodium chloride (% w/w)	0	0.08	0.2	0.4	0.9
Osmotic pressure (mOsm)	5	30	72	128	290
B.A. (%)	63	47	16	13	7

The osmotic pressure was controlled by addition of sodium chloride.

The medicament bioavailability was unexpectedly increased according to decrease in the osmotic pressure of less than 290 mOsm.

Composition No.1, 5-7 and 12-13

(Osmotic pressure-controlling agent : Glucose)

Composition No.	1	5	6	7	12	13
Glucose(% w/w)	0	0.5	1.2	2.1	5	67
Osmotic pressure (mOsm)	5	30	72	128	340	4000
B.A. (%)	63	29	10	9	7	4

The osmotic pressure was controlled by addition of glucose.

The medicament bioavailability was unexpectedly increased according to decrease in the osmotic pressure of less than 290 mOsm.

Composition No.1, 8-10 and 14 (Osmotic pressure-controlling agent: Free)

Composition No.	10	1	9	8	14
Crystalline cellulose (% w/w)	2.7	1.5	0.4	0.1	0
Carmellose sodium (% w/w)	0.3	0.2	0.1	0	0.2
Osmotic pressure (mOsm)	7	5	0	0	5
B.A. (%)	53	63	37	22	7

Crystalline cellulose carmellose sodium consists of crystalline cellulose and carmellose sodium. (crystalline cellulose / carmellose sodium = 89 / 11)

Carboxy methyl cellulose sodium is a synonym of carmellose sodium.

Water insoluble substance contained compositions (1 and 8-10) showed increased bioavailability accompany with the water insoluble substance concentration increase up to 1.5%w/w.

On the contrary, water insoluble substance free composition (14) did not show increased medicament bioavailability. It can be concluded that low water soluble or water insoluble substance would be necessary for this invention.

Composition No.2, 5 and 15-16

(Osmotic pressure-controlling agent: Sodium Chloride or Glucose)

Composition No.	2	15	5	16
Crystalline cellulose (% w/w)	1.5	0	1.5	0
Carmellose sodium (% w/w)	0.2	0.2	0.2	0.2
Sodium chloride (% w/w)	0.08	0.08	0	0
Glucose (% w/w)	0	0	0.5	0.5
Osmotic pressure (mOsm)	30	30	30	30
B.A. (%)	47	5	29	5

The osmotic pressures of these compositions were adjusted to 30 mOsm.

The medicament bioavailabilities were increased by the osmotic pressure of 30 mOsm only when the composition contained the water insoluble substance.

ii. Example 2 and Comparative example 2 (page 16, line 4 to page 18, line 3)

Medicament: 5-Carboxy fluorescein

A model drug of the water-soluble low molecular weight drug

- Osmotic pressure of less than 290 mOsm unexpectedly increased the medicament bioavailability.
- Low water soluble or water insoluble substances were necessary to increase the medicament bioavailability.

Composition No.17-18 and 19-20 (Osmotic pressure-controlling agent: Glucose)

Composition No.	17	18	19	20
Glucose (% w/w)	0	0.4	5	67
Osmotic pressure (mOsm)	6	30	340	4000
B.A. (%)	52	47	5	3

The osmotic pressure was controlled by addition of glucose.

The medicament bioavailability was unexpectedly increased according to decrease in the osmotic pressure of less than 290 mOsm.

Composition No.17-18 and 21-22 (Osmotic pressure-controlling agent: Glucose)

Composition No.	17	18	21	22
Crystalline cellulose (% w/w)	1.5	1.5	0	0
Carmellose sodium (% w/w)	0.2	0.2	0.2	0.2
Glucose (% w/w)	0	0.4	0	0.4
Osmotic pressure (mOsm)	6	30	6	30
B.A. (%)	52	47	7	3

The medicament bioavailability of water insoluble substance contained compositions (17 and 18) were unexpectedly increased according to decrease in the osmotic pressure of less than 290 mOsm. On the contrary, water insoluble substance free compositions (21 and 22) did not increase the medicament permeability. It can be concluded that low water soluble or water insoluble substance would be necessary for this invention.

iii. Example 3 and Comparative example 3 (page 18, line 4 to page 20, line 3)

Medicament: Salmon calcitonin

A model drug of the water-soluble high molecular weight drug

- Osmotic pressure of less than 290 mOsm unexpectedly increased the medicament bioavailability.
- Low water soluble or water insoluble substances were necessary to increase the medicament bioavailability.

Composition No.23-24 and 25-26 (Osmotic pressure-controlling agent: Glucose)

Composition No.	23	24	25	26
Glucose (% w/w)	0	0.4	5	67
Osmotic pressure (mOsm)	10	30	340	4000
B.A. (%)	52	47	3	2

The osmotic pressure was controlled by addition of glucose.

The medicament bioavailability was unexpectedly increased according to decrease in the osmotic pressure of less than 290 mOsm.

Composition No.23-24 and 27-28 (Osmotic pressure-controlling agent: Glucose)

Composition No.	23	24	27	28
Crystalline cellulose (% w/w)	1.5	1.5	0	0
Carmellose sodium (% w/w)	0.2	0.2	0.2	0.2
Glucose (% w/w)	0	0.4	0	0.4
Osmotic pressure (mOsm)	10	30	6	30
B.A. (%)	52	47	5	5

The medicament bioavailability of water insoluble substance contained compositions (23 and 24) were unexpectedly increased according to decrease in the osmotic pressure of less than 290 mOsm. On the contrary, water insoluble substance free compositions (27 and 28) did not increase the medicament permeability. It can be concluded that low water soluble or water insoluble substance would be necessary for this invention.

3. **Comparison of examples and comparative examples concerning subject matter (2)**

Example 4 and comparative example 4

(page 23, line 29 to page 26, line8)

Medicament: Fluorescein

A model drug of the liposoluble low molecular weight drug

Hemostatic agent: Carbazochrome or Tranexamic acid

- The medicament retainability was increased in the presence of a hemostatic agent to provide the decreased medicament bioavailability.

Composition No.29-33 (Osmotic pressure-controlling agent: Sodium chloride)

Composition No.	29	30	31	32	33
Sodium chloride (% w/w)	0	0.08	0.2	0.4	0
Carbazochrome (% w/w)	0.1	0.1	0.1	0.1	0
Tranexamic acid (% w/w)	0	0	0	0	0.1
Osmotic pressure (mOsm)	5	30	72	128	7
B.A. (%)	30	22	10	7	28
Residual ratio (%)	49	32	10	9	51

The osmotic pressure was controlled by addition of sodium chloride.

Composition No.34-37 (Osmotic pressure-controlling agent: Sodium chloride)

Composition No.	34	35	36	37
Sodium chloride (% w/w)	0	0.08	0.2	0.4
Carbazochrome (% w/w)	0	0	0	0
Tranexamic acid (% w/w)	0	0	0	0
Osmotic pressure (mOsm)	5	30	72	128
B.A. (%)	63	47	16	13
Residual ratio (%)	23	15	5	4

The osmotic pressure was controlled by addition of sodium chloride.

The medicament retainability was increased in the presence of a hemostatic agent to provide the decreased medicament bioavailability.

Fig.1

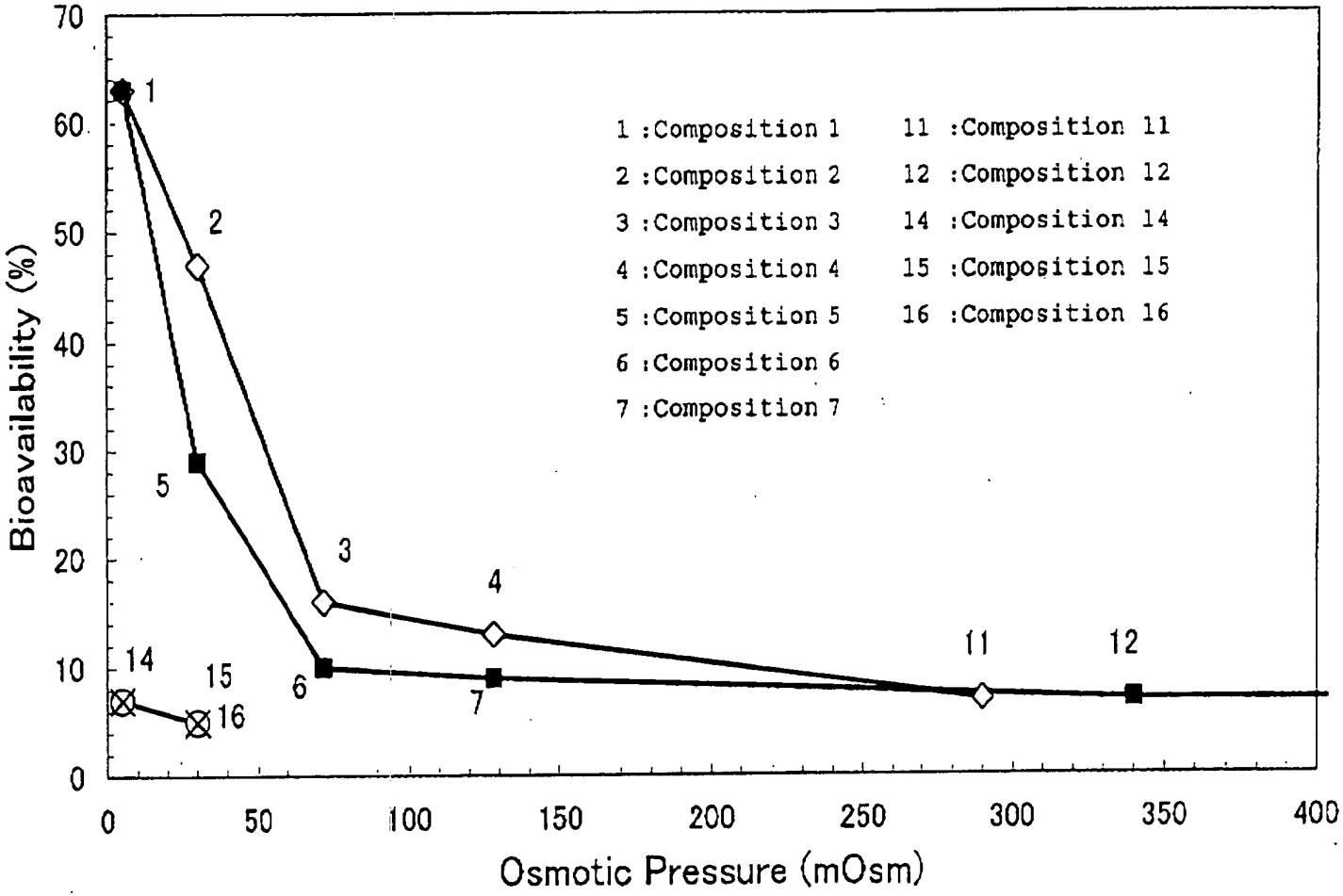

Bioavailability (%)
Osmotic Pressure (mOsm)
0
10
20
30
40
50
60
70
0
50
100
150
200
250
300
350
400
1 :Composition 1
2 :Composition 2
3 :Composition 3
4 :Composition 4
5 :Composition 5
6 :Composition 6
7 :Composition 7
11 :Composition 11
12 :Composition 12
14 :Composition 14
15 :Composition 15
16 :Composition 16
1
2
3
4
5
6
7
11
12
14
15
16

Fig.2

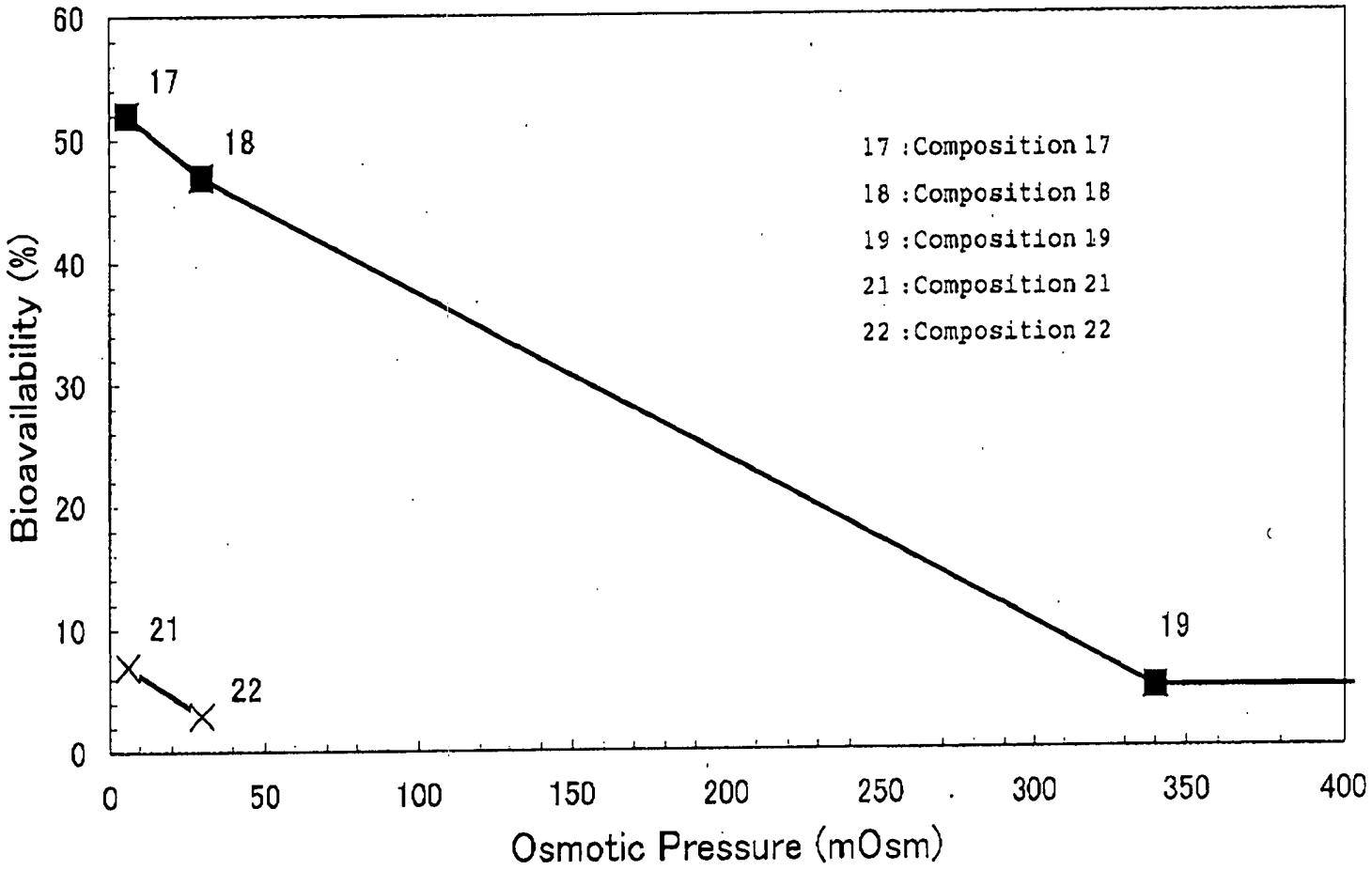
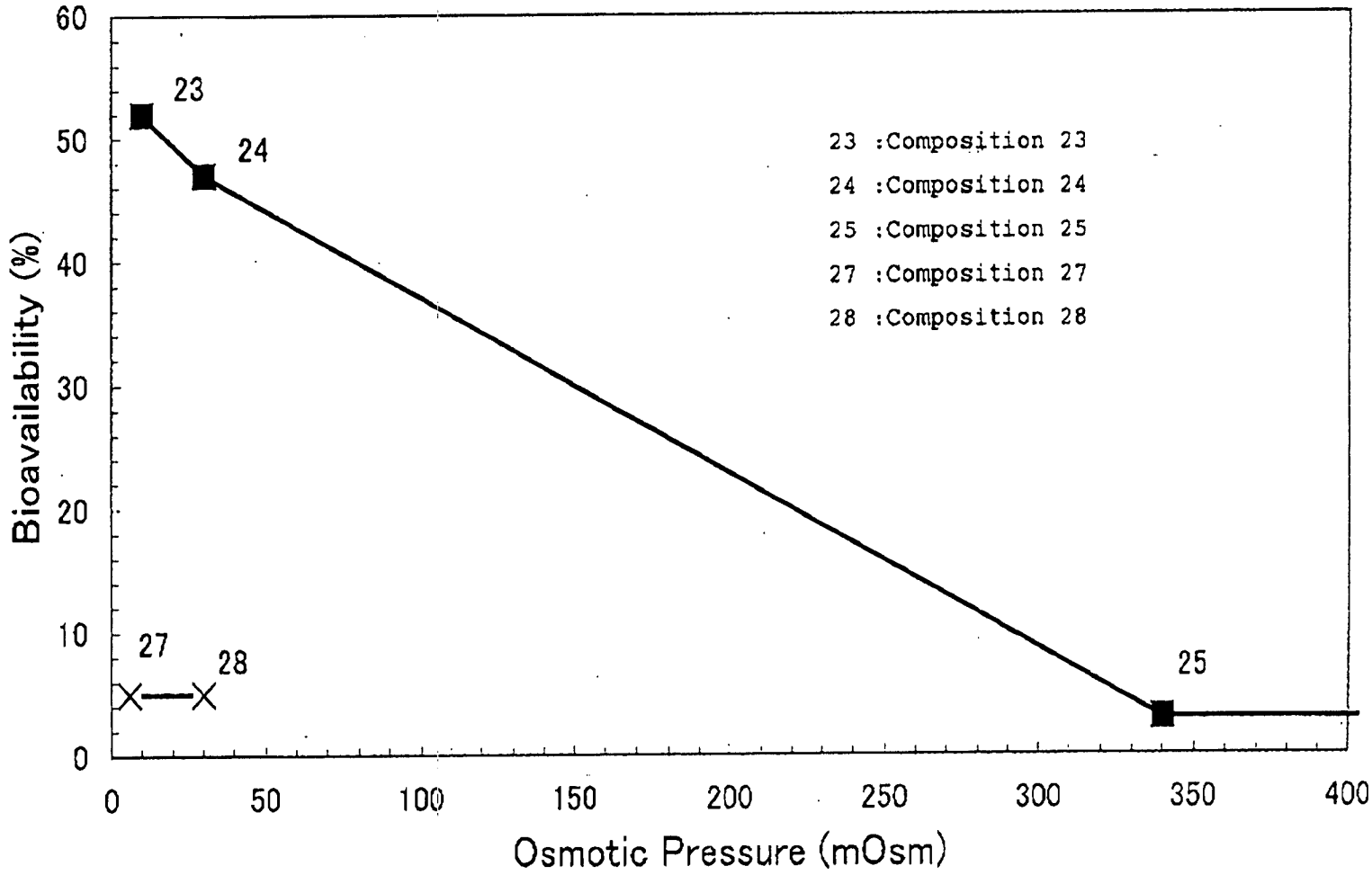

60
50
40
30
20
10
0
Bioavailability (%)
17
18
19
21
22
17 :Composition 17
18 :Composition 18
19 :Composition 19
21 :Composition 21
22 :Composition 22
0
50
100
150
200
250
300
350
400
Osmotic Pressure (mOsm)

Fig.3


60
50
40
30
20
10
0
Bioavailability (%)
0
50
100
150
200
250
300
350
400
Osmotic Pressure (mOsm)
23
24
25
27
28
23 :Composition 23
24 :Composition 24
25 :Composition 25
27 :Composition 27
28 :Composition 28